We conclude that non-A, non-B hepatitis after blood transfusion from a largely British blood donor group probably leads to clinically significant chronic liver disease very rarely indeed.

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Chloramphenicol toxicity in neonates: its incidence and prevention

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Abstract

The incidence of dose related chloramphenicol toxicity was determined in 64 neonates from 12 hospitals. Ten of the 64 exhibited symptoms attributed clinically to chloramphenicol toxicity. Nine received the dose prescribed and one an overdose. Symptoms of the grey baby syndrome were observed in five of the 10 babies; four babies suffered reversible haematological reactions; and one baby was described as very grey. Peak serum chloramphenicol concentrations in these 10 babies ranged from 28 to 180 mg/l and trough concentrations from 19 to 47 mg/l. Serum chloramphenicol concentrations above the therapeutic range (15-25 mg/l) were observed in a further 27 neonates (two had received a 10-fold overdose), none of whom showed signs of toxicity.

Serious toxicity was associated with either prescription of dosages greater than that recommended or overdosage of chloramphenicol. High concentrations in young neonates may be avoided by prescribing and giving the recommended dose and then careful monitoring; concentrations should be maintained between 15 and 25 mg/l. No babies with concentrations within this range showed clinical signs of toxicity.

Introduction

Despite concern about its toxicity chloramphenicol is widely used to treat neonatal meningitis.[1] Three types of toxicity have been described—namely, the grey baby syndrome,[2] reversible dose related haemopoietic disturbances,[3] and idiopathic marrow aplasia unrelated to dosage.[4] Serum chloramphenicol concentrations between 40 and 200 mg/l have been reported in association with the grey syndrome,[5 6] and reversible bone marrow suppression related to dosage may occur when serum concentrations exceed 25 mg/l.[3] Irreversible marrow aplasia is a rare complication (incidence 1/20 000 to 1/80 000 patients treated) and has a high mortality. Its occurrence is unpredictable.

The incidence of dose related chloramphenicol toxicity in the newborn is unknown. There is no general agreement on the desirable therapeutic range of chloramphenicol concentrations, but serum concentrations of 10-20 mg/l[7] and 15-25 mg/l[8] are often quoted. As the minimum inhibitory concentration of chloramphenicol for some Gram negative rods may be as high as 6 mg/l and only 30-60% of the drug crosses the meninges it would seem more appropriate to maintain serum concentrations in the range 15-25 mg/l provided that such concentrations are not associated with toxic manifestations.

In this study, which was carried out between March 1978 and August 1981, we determined the incidence of dose related chloramphenicol toxicity in 64 neonates receiving chloramphenicol for life threatening infections. We assessed the value of measuring serum concentrations of the drug and the possibility of predicting toxic effects and establishing the therapeutic range of chloramphenicol concentrations.

Patients and methods

Study population—We studied 64 neonates (less than 28 days old) from 12 hospitals who formed part of a larger study on the penetration of antibiotics in neonatal meningitis.[1 9] Their gestational ages ranged from 26 to 40 weeks and their birth weights from 770 to 4420 g. All the babies were scrutinised during treatment for signs and symptoms of the grey baby syndrome—that is, vomiting, respiratory distress, abdominal distension, ashen grey cyanosis, flaccidity, and cardiovascular collapse. Adverse haematological reactions were also sought.

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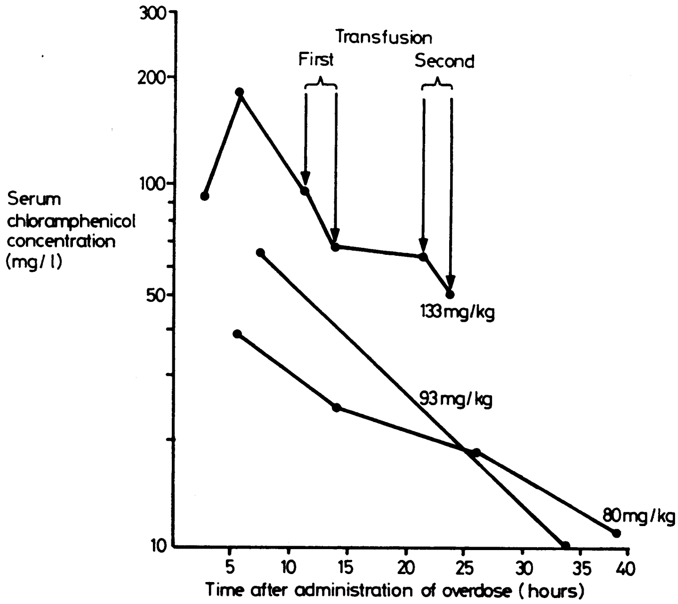
Dosage and assay of chloramphenicol—The prescribed dosage of chloramphenicol and any subsequent adjustments were decided by the referring paediatricians. Chloramphenicol was administered intravenously on 91 occasions, intramuscularly on 14, and by mouth on 13. Concentrations of active chloramphenicol were determined in 205 timed specimens of serum by methods described elsewhere.[10] Chloramphenicol esters and metabolites were not measured by this method. Opinion varies on the time to peak serum chloramphenicol concentration in the neonate[8,11-13]; in this study the term peak concentration applies to samples collected 15 minutes to one hour after intravenous administration, 30 minutes to two hours after intramuscular administration, and one to four hours after oral administration. Recommended doses were taken as 25 mg/kg/day for preterm and term babies in the first week of life and 37·5-50 mg/kg/day for term babies older than seven days.[14]

Results

Ten of the 64 babies had symptoms that were attributed clinically to chloramphenicol toxicity. Nine received the prescribed dose, although in six this was greater than that recommended (table I). One baby received a 10-fold overdose. Four of the nine babies collapsed suddenly, became grey, and suffered cardiac arrest within 48 hours after the first dose of chloramphenicol (table I). The drug was stopped in two of these four babies, one of whom gradually improved over the next 72 hours. The second remained stable for six hours but then rapidly deteriorated with cardiac and respiratory arrest and died. Postmortem examination showed an intraventricular haemorrhage. Dosage was reduced in the other two neonates. One showed a rapid deterioration, developed disseminated intravascular coagulation, and suffered several fits; he survived, but with neurological sequelae. The other, who had *E coli* meningitis, died three days later. Four babies developed adverse haematological reactions three to 10 days after the start of treatment, thrombocytopenia developing in three and neutropenia in one. Haematological values in all four returned to normal after chloramphenicol treatment was reduced or stopped. The last baby was described as very grey after 14 days' treatment, and the antibiotic was stopped. Serum concentrations at this time were within the range 15-25 mg/l, although previous concentrations had been high. Peak serum chloramphenicol concentrations in the nine babies exhibiting toxic symptoms ranged from 28 to 140 mg/l, and trough concentrations were in the range 19 to 47 mg/l.

Four accidents regarding the use of chloramphenicol were recorded. A 10-fold overdose was administered to three babies. For the first neonate 13·3 mg/kg every six hours (53 mg/kg/day) was prescribed, and the baby received 10 times this amount on two occasions. A serum concentration of 180 mg/l was recorded six hours after the second overdose, and his condition rapidly deteriorated with appreciable bradycardia and no urine output. He received two exchange transfusions, but the serum concentration was still high at 51 mg/l, and cardiac arrest and death ensued 31 hours after the second overdose. Cause of death was recorded as acute suppurative encephalitis and chloramphenicol toxicity. The figure shows the effects of the two exchange transfusions on serum chloramphenicol concentrations.



Serum chloramphenicol concentrations over time, and dosages administered, in three babies who received overdoses.

The second baby, for whom 9·3 mg/kg every six hours (37 mg/kg/day) was prescribed, showed no symptoms of toxicity despite having a serum concentration of 65 mg/l seven and a half hours after the overdose. The remaining neonate (prescribed dose 24 mg/kg/day) received a dose of 80 mg/kg. The only adverse effect was acidosis, and after 40 hours treatment was restarted. Blood chloramphenicol concentration five hours after the overdose was 40 mg/l. Serum chloramphenicol concentrations below 25 mg/l were recorded in both these latter babies within 14-22 hours. The figure shows the concentration time curves in these three neonates. One baby received 40 mg

TABLE I—*Signs of toxicity in nine neonates receiving chloramphenicol*

Case No	Evidence of toxicity	Dose (mg/kg/day)	Recommended dose[14] (mg/kg/day)	Serum concentration (mg/l)	Time after dose (hours)
1	Sudden collapse, grey coloration, cardiac and respiratory difficulties	34	25	>38 >80 4	4·5 25 92
2	Sudden collapse, grey coloration, cardiac and respiratory difficulties	53	25	35	2
3	Sudden collapse, grey coloration, cardiac and respiratory difficulties	77 77 41	25	>60 140* 124* 90	7·5 5* 7·5* 7
4	Sudden collapse, grey coloration, cardiac and respiratory difficulties	50 36 36	25	31 46 35 >43	12 0·5 12 6
5	Haematological	22	25	45 36 40	1 12 1
6	Haematological	50	25	38 47 47	12 1 12
7	Haematological	25	25	19 34 30 56	12 1 12 1
8	Haematological	37·5	37·5-50	72 100	1 3
9	Very grey	29	25	21 28 10	12 0·5 24

*Values before and after exchange transfusion.

chloramphenicol intraventricularly instead of intravenously. The concentration of chloramphenicol in cerebrospinal fluid 18 hours later was 52 mg/l, although the serum concentration at this time was only 3 mg/l. The patient was lost to follow up.

High serum concentrations, which may have been the result of an unrecognised overdose, were observed in four babies. Two of these (cases 1 and 8, table I) suffered toxic effects. The other two, who were prescribed 60 and 50 mg/kg/day (recommended dosage 37·5 and 25 mg/kg/day respectively), showed no signs of toxicity despite a peak concentration of 90 mg/l in one and a concentration of 31 mg/l 17 hours after injection in the other. The remaining 49 babies showed no obvious toxic signs or symptoms resulting from chloramphenicol treatment. Table II shows serum chloramphenicol concentrations and dosage schedules in 45 of these neonates; data from four babies could not be evaluated. Peak chloramphenicol concentrations >25 mg/l or trough concentrations >15 mg/l, or both, were observed in 23 of these neonates, 16 of whom were given more than the recommended dose. Three of these babies had concentrations greater than 50 mg/l. Table III shows the relation between dosage, high serum concentrations, and toxicity.

The 10 babies who showed signs of chloramphenicol toxicity had normal renal function before treatment. During treatment oedema, hyponatraemia, and reduced urine output were recorded in four, two of whom were found later to have inappropriate secretion of antidiuretic hormone.

TABLE II—*Dosage schedules and serum chloramphenicol concentrations in 45 neonates who did not show any signs of toxicity*

Dosage given	Serum chloramphenicol concentrations			Total
	Peak <15 mg/l	Peak 15-25 mg/l trough <15 mg/l	Peak >25 mg/l trough >15 mg/l	
Recommended[14]	4	4	3	11
> Recommended	1	3	16	20
< Recommended	9	1	4	14
Total	14	8	23	45

TABLE III—*Relation between dosage, high serum concentrations, and toxicity*

	No	Peak concentration >25 mg/l or trough >15 mg/l or both	Clinical signs or symptoms of toxicity
Prescribed dose	54	32	9*
Known overdose	4	3+1 (CSF)	1
?Overdose	2	2	
Not evaluated	4		
Total	64	37+1 (CSF)	10

CSF = Cerebrospinal fluid.
*All nine babies had peak concentrations >25 mg/l or trough concentrations >15 mg/l, or both. In two cases an overdose was suspected.

Discussion

The present study has shown that many neonates (27/37) can tolerate serum chloramphenicol concentrations above 25 mg/l with no clinical signs of toxicity. Seven of these 27 babies had serum concentrations in excess of 50 mg/l. No relation could be established between the duration of high serum concentrations and toxicity. The effect of high serum concentrations may be related to age, as nine of the 10 babies who showed toxic signs were less than nine days old while four of the seven with serum concentrations >50 mg/l but no toxicity were more than 20 days old. High serum concentrations in the absence of toxicity have been reported in a 10 week old baby.[15]

Our results suggest that chloramphenicol may be used safely to treat neonates if serum concentrations are maintained in the range 15-25 mg/l, as no babies with concentrations in this range showed signs of toxicity. Symptoms of the grey syndrome were associated with very high serum concentrations (35-180 mg/l), which are unlikely to occur unless an overdose has been administered or the prescribed dosage is well above that recommended. Reversible haematological side effects occurred at lower serum concentrations, which were nevertheless outside the therapeutic range, and were not associated with prolonged treatment. Predicting those at risk of haematological effects is difficult.

The delayed clearance of chloramphenicol in neonates is thought to be due to inefficient glucuronidisation in the liver and reduced renal elimination of the metabolite.[16] Poor renal function would result in both reduced elimination of active chloramphenicol by glomerular filtration and reduced elimination of the parent ester, which would remain in the body and subsequently undergo hydrolysis to active drug. Our results indicate that one manifestation of the grey syndrome is reduced renal output resulting in persistent high serum concentrations. Probably poor renal function is just as important as low activities of liver enzymes in maintaining high chloramphenicol concentrations.

The assertion that active chloramphenicol, rather than the parent compound or its metabolites, causes toxicity in the neonate is widely accepted but is based on indirect evidence. Adult patients with anuria accumulate high concentrations of glucuronide metabolite with no evidence of toxicity,[17] and large doses of chloramphenicol glucuronide have been administered to rats without toxic reactions. Chloramphenicol glucuronide concentrations in neonates have not been determined.

Tenfold overdoses administered to three babies in this study were the result of the decimal point being misread when the injections were drawn up from a 1·2 g phial (100 g/l). When such a concentrated solution is used unrealistically small volumes are required for six hourly administration to small babies; a 300 mg paediatric preparation is now available. The severity of the symptoms suffered by the three babies correlated with the measured concentrations of chloramphenicol in their blood. Young neonates are capable of withstanding and surviving high concentrations of chloramphenicol for short periods, although if excessively high concentrations persist death may result.

Multiple exchange transfusions have been advocated as effective treatment for severe chloramphenicol intoxication,[18] but two exchange transfusions in one subject in the present study (figure) had little effect on serum chloramphenicol concentrations. Charcoal column haemoperfusion has been used with dramatic effect in one term neonate, reducing serum concentrations from 98 mg/l to 13·5 mg/l in three hours, but this treatment may have side effects.[19]

In the present study serious toxicity was associated with either overprescription or overdosage of chloramphenicol in most cases. Thus high serum chloramphenicol concentrations and their associated toxicity in young neonates may be avoided by prescribing the recommended dose initially[1 14] and then monitoring blood concentrations and haematological values every 48 hours. The microbiological method used in this study is within the competence of any routine clinical laboratory and yields results in five hours. Particular attention should be paid to babies with poor renal and liver function, and extreme care must be exercised to avoid arithmetic errors when preparing injections.

We thank the paediatricians at the following hospitals for allowing us to study their patients and for providing the clinical information contained in this paper, and the microbiologists for their support: Bromley Hospital, Bromley; Farnborough Hospital, Orpington; Hammersmith Hospital, London; Horton General Hospital, Banbury; John Radcliffe Hospital, Oxford; King's College Hospital, London; Lewisham Hospital, London; Northwick Park Hospital, Harrow; Queen Charlotte's Maternity Hospital, London; Queen Elizabeth's Hospital for Sick Children, London; St Helier Hospital, Carshalton; and the Hospital for Sick Children, London.

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SHORT REPORTS

Do some marathon runners bleed into the gut?

Bleeding into the bladder wall and exercise related haematuria are recognised complications of marathon running.[1] Bleeding may also occur into the bowel[2] and perhaps caecal wall.[3] I report a study of runners in a provincial marathon race.

Patients, methods, and results

I posted questionnaires to the 600 runners who registered for the 1983 Guildford marathon. The questionnaires established the age, sex, number of previous marathons, weekly training milage, and the presence of gastrointestinal symptoms and blood in vomit, urine, and stools. Of the 600 runners 415 showed their intention to run the full marathon by entering the second circuit of the course, and 386 completed the race. Of the 415 (287 men and 12 women) 299 (72%) returned their questionnaires. In a preliminary study three runners who had taken part in a different marathon and were not entered for the Guildford marathon submitted to a hospital laboratory stool specimen taken before and after the marathon race. One of these three runners (a slow veteran) gave positive results for melaena after the race, though not before. He later ran in another marathon and again these results became positive.

In this study 10% of the original applicants were randomly selected and asked to test their urine for the presence of blood immediately after the race with a reagent strip (Labstix) and to provide stool smears taken before and after the race to test for the presence of occult blood (Hema-Chek). Samples were returned by 36 runners (about 54% of those eligible). None of them reported frank haematuria, but two had reagent strips giving positive results. These, however, do not discriminate between red blood cells, haemoglobin from march haemoglobinuria, or myoglobin, which may be produced in quantity during vigorous exercise.[4] Only one runner (a young slow man) reported tarry stools. Two men (one young and fast, and one a slow veteran) with negative test results for melaena before the race gave definitely positive results after it. A further man (young and fast) had a weakly positive smear after the race. None of the smears was positive before the race. One runner gave positive results with both the urine reagent strip and stool smear. None of the runners with a positive stool smear result admitted to piles.

Comment

Only one of the 299 runners studied noted a tarry stool, but three (8%) of 39 (including those in the preliminary study) passed stools after racing which gave positive results for melaena. This suggests that unrecognised bleeding into the gut during a marathon is not uncommon. Contributory factors may include an unsuspected local cause such as piles, damage to intraabdominal hollow organs from repetitive impact of a free surface against a fixed surface such as has been described for the bladder,[1] relative ischaemia of the gut wall caused by diversion of the splanchnic circulation,[2] and trauma haemolysis in the feet which might trigger disseminated intravascular coagulation with some consumption of coagulation factors and cause a predisposition to bleeding. The aetiology of the mild anaemia found in some distance runners is obscure,[5] but repeated oozing into the gut during training and racing may be a factor.

I thank the Guildford Lions and the marathon runners for their help and cooperation, Ames Ltd for diagnostic aids, and Dr J Shirley for advice. The study was financed by a grant from the research foundation of the Royal College of General Practitioners.

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Skin test wheal size and erythema not reduced by topical antihistamine

Prior treatment with systemic antihistamine preparations suppresses pruritus induced by histamine[1] and allergens[2] and diminishes wheal size.[3] It is common practice to apply a topical antihistamine preparation for symptomatic relief after skin testing with allergens, although the benefits of this have not been tested. We report a double blind controlled trial of mepyramine maleate cream versus placebo cream applied after skin testing in patients with atopy.

Patients, methods, and results

Skin prick tests were performed on both arms of 32 patients with atopy using the following Bencard allergens: house dust mite, grass and tree pollen, cat and dog fur, feathers, and aspergillus; positive (histamine) and negative controls were also used. After 10 minutes we recorded the diameter in millimetres of the largest wheal and the intensity of erythema on a visual analogue scale ranging fron "no erythema" to "intense erythema" on a 100